UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/525,699	02/22/2005	Peter C.M. Van Zijl	PKRY 200001US01	7645

27885 7590 10/26/2010

FAY SHARPE LLP
1228 Euclid Avenue, 5th Floor
The Halle Building
Cleveland, OH 44115

EXAMINER	
JUNG, UNSU	

ART UNIT	PAPER NUMBER
3768	

MAIL DATE	DELIVERY MODE
10/26/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,699	VAN ZIJL ET AL.	
	Examiner	Art Unit	
	UNSU JUNG	3768	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 December 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,12-16,18-20,22-24 and 29-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,12-16,18-20,22-24 and 29-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 February 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Examiner for the current application has been changed from Salieu M. Abraham to Unsu Jung in Art Unit 3768. Any inquiry concerning this application should be directed to Unsu Jung, whose contact information is provided in the conclusion section of this Office Action.

Response to Amendment

2. Applicant's amendments in the reply filed on December 10, 2009 have been acknowledged and entered. The reply included amendments to claims 1-5 and 23.

Status of Claims

3. Claims 1-5, 12-16, 18-20, 22-24, and 29-34 are pending and currently under consideration for patentability under 37 CFR 1.104.

Priority

4. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. The instant application is a national phase under 35 U.S.C. 371 of PCT International Application No. PCT/US2003/026580, filed on August 26, 2003.

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copies of U.S. Provisional Patent Application Serial No. 60/406,040, filed on August 27, 2002 has been filed in the PCT/US2003/026580.

Rejections Withdrawn

5. The rejection of claims 1-5, 12-16, 18-20, 22-24 and 29-31 under 35 U.S.C. 112, first paragraph has been withdrawn in view of the amended independent claims 1 and 23 in the reply filed on December 10, 2009.

6. The rejection of claims 1-5, 12-16, 18-20 and 22 under 35 U.S.C. 112, second paragraph has been withdrawn in view of the amended independent claims 1 and 23 in the reply filed on December 10, 2009.

7. The rejection of claims 1- 5, 12, 22 -24, 27, and 31 under 35 U.S.C. 102(b) as being anticipated by Song et al. (*Magnetic Resonance in Medicine*, 2002, Vol. 47, pp616-620) has been withdrawn as Song et al. does not teach determination of a microvascular blood volume.

Claim Objections

8. Claims 29 and 30 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 29 and 30 depend from independent claim 23, which currently recites all the limitations currently recited in claims 29 and 30.

35 USC § 112, Sixth Paragraph

9. The following is a quotation of the sixth paragraph of 35 U.S.C. 112:

> An element in a claim for a combination may be expressed as a means or step for performing a specified function without the recital of structure, material, or acts in support thereof, and such claim shall be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof.

10. The following means-plus-function limitations of claims 23, 24, and 29-31 invoke 35 U.S.C. 112, sixth paragraph:

- Blood signal reduction means for performing a blood signal reduction magnetic resonance excitation sequence that substantially reduces a magnetic resonance signal from blood while retaining an effective parenchymal tissue signal recited in claim 23
- Readout means for performing a readout magnetic resonance sequence to acquire a magnetic resonance signal arising predominantly from parenchymal tissue, the readout means operating subsequent to operation of the blood signal reduction means recited in claim 23
- Reconstruction means for generating a reconstructed image from the acquired magnetic resonance signal recited in claim 23
- Means for computing a blood volume parameter value from the reconstructed image and means for computing the blood volume from the tissue-normalized reconstructed image recited in claims 23 and 29

- Means for normalizing the reconstructed image based on a T1 value of tissue to generate a tissue-normalized reconstructed image recited in claims 23 and 29
- Means for computing an intermediate parameter functionally related to blood volume for a plurality of reconstructed images produced by repetitively invoking the readout means and the reconstruction means with a corresponding plurality of echo times recited in claims 23 and 30
- Means for fitting a parameterized model to the intermediate parameters and the corresponding echo times, the parameterized model having parameters including a rest blood volume and a blood volume change recited in claims 23 and 30
- Inversion recovery means for performing an inversion recovery magnetic resonance excitation sequence having an inversion time effective to produce a substantially reduced blood signal recited in claim 24
- Means for combining the reconstructed image with a reference image to identify an abnormality in the reconstructed image recited in claim 31

11. The following means-plus-function limitations have been interpreted in light of the specification:

For blood signal reduction means for performing a blood signal reduction magnetic resonance excitation sequence that substantially reduces a magnetic

resonance signal from blood while retaining an effective parenchymal tissue signal" recited in claim 23, the specification discloses the following:

> The approach uses an inversion recovery magnetic resonance excitation sequence having an inversion time 60 optimized for substantial nulling of the blood signal based on a blood T1 value particular to a certain magnetic field strength and hematocrit range (PG Pub. paragraph [0022]). The inversion recovery magnetic resonance excitation sequence substantially nulls the signal from blood so that the magnetic resonance signal corresponds predominantly to tissue, with substantially negligible contribution of blood (PG Pub. paragraph [0022]).

For readout means for performing a readout magnetic resonance sequence to acquire a magnetic resonance signal arising predominantly from parenchymal tissue, the readout means operating subsequent to operation of the blood signal reduction means recited in claim 23, the specification discloses the following:

> FIG. 2 diagrammatically shows a suitable magnetic resonance imaging pulse sequence employing a blood-nulling inversion recovery magnetic resonance excitation sequence 70 to null the blood signal, and an exemplary single shot echo planar imaging readout 72 (PG Pub. paragraph [0026]). Note that the echo planar imaging readout is exemplary only, and does not exclude employing additional or other magnetic resonance imaging, magnetic resonance spectroscopy or localized spectroscopy detection schemes (PG Pub. paragraph [0029]).

For reconstruction means for generating a reconstructed image from the acquired magnetic resonance signal recited in claim 23, the specification discloses the following:

> A reconstruction processor 44 performs a Fourier transform-based image reconstruction or other type of image reconstruction to generate one or more reconstructed images from the stored k-space magnetic resonance samples (PG Pub. paragraph [0020]).

For means for computing a blood volume parameter value from the reconstructed image and means for computing the blood volume from the tissue-normalized reconstructed image recited in claims 23 and 29, the specification discloses the following:

> FIG. 3 shows a block diagram of an exemplary processor 100 that computes a rest blood volume BV_{rest} and a blood volume change (PG Pub. paragraph [0048]). A rest blood volume BV_{rest} calculator 116 computes the rest blood volume (PG Pub. paragraph [0049]).

For means for normalizing the reconstructed image based on a T1 value of tissue to generate a tissue-normalized reconstructed image recited in claims 23 and 29, the specification discloses the following:

> Normalization processor 140 normalizes the image stored in the image memory 46 to produce a normalized image 142 (PG Pub. paragraph [0055]).

For inversion recovery means for performing an inversion recovery magnetic resonance excitation sequence having an inversion time effective to produce a substantially reduced blood signal recited in claim 24, the specification discloses the following:

> The approach uses an inversion recovery magnetic resonance excitation sequence having an inversion time 60 optimized for substantial nulling of the blood signal based on a blood T1 value particular to a certain magnetic field strength and hematocrit range (PG Pub. paragraph [0022]). The inversion recovery magnetic resonance excitation sequence substantially nulls the signal from blood so that the magnetic resonance signal corresponds predominantly to tissue, with substantially negligible contribution of blood (PG Pub. paragraph [0022]).

The above means-plus-function limitations have been interpreted as the corresponding structures disclosed in the specification or any equivalent structures thereof in light of the specification for the purpose of examination.

12. For the following means-plus-function limitations, the specification fails to provide corresponding structures.

- Means for computing an intermediate parameter functionally related to blood volume for a plurality of reconstructed images produced by repetitively invoking the readout means and the reconstruction means with a corresponding plurality of echo times recited in claims 23 and 30
- Means for fitting a parameterized model to the intermediate parameters and the corresponding echo times, the parameterized model having parameters including a rest blood volume and a blood volume change recited in claims 23 and 30
- Means for combining the reconstructed image with a reference image to identify an abnormality in the reconstructed image recited in claim 31

The above means-plus-function limitations have been given the broadest reasonable interpretation.

Claim Rejections - 35 USC § 112

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 23, 24, and 29-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claims 23, 31, and all dependent claims thereof, the terms "means for computing an intermediate parameter functionally related to blood volume for a plurality of reconstructed images produced by repetitively invoking the readout means and the reconstruction means with a corresponding plurality of echo times", "means for fitting a parameterized model to the intermediate parameters and the corresponding echo times, the parameterized model having parameters including a rest blood volume and a blood volume change", and "means for combining the reconstructed image with a reference image to identify an abnormality in the reconstructed image" are vague and indefinite. As set forth above, claims 23, 31, and all dependent claims thereof recite various "means for" clauses. The specification as filed does not set forth specific structures for performing the means recited. The "means for computing an intermediate parameter functionally related to blood volume for a plurality of reconstructed images produced by repetitively invoking the readout means and the reconstruction means with a corresponding plurality of echo times", "means for fitting a parameterized model to the intermediate parameters and the corresponding echo times, the parameterized model having parameters including

a rest blood volume and a blood volume change", and "means for combining the reconstructed image with a reference image to identify an abnormality in the reconstructed image" all lack specific related structures in the specification. See MPEP § 2181 for guidance in determining whether an applicant has complied with the requirements of 35 U.S.C. 112, second paragraph, when 35 U.S.C. 112, sixth paragraph, is invoked. 35 U.S.C. 112, sixth paragraph states that a claim limitation expressed in means-plus-function language "shall be construed to cover the corresponding structure…described in the specification and equivalents thereof." "If one employs means plus function language in a claim, one must set forth in the specification an adequate disclosure showing what is meant by that language. If an applicant fails to set forth an adequate disclosure, the applicant has in effect failed to particularly point out and distinctly claim the invention as required by the second paragraph of section 112." *In re Donaldson Co.*, 16 F.3d 1189, 1195, 29 USPQ2d 1845, 1850 (Fed. Cir. 1994) (*in banc*).

B. Claims 32 and all dependent claims thereof are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: assessing microvascular blood volume. The preamble of claim 32 recites "a magnetic resonance method for assessing microvascular blood volume." However, claim 32 and all dependent claims thereof lack any step of assessing microvascular blood volume, which is necessary to perform the

intended purpose of the claimed method as the preamble recites "a magnetic resonance method for assessing microvascular blood volume."

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

17. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 1-3, 12, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miyazaki (U.S. Patent No. 7,254,437 B2, filed Apr. 16, 1999) in view of Ostergaard (WO 00/57777, Oct. 5, 2000).

With respect to claim 1, Miyazaki teaches a magnetic resonance imaging (MRI) system includes an ECG detector for the patient object being imaged and an element for performing an MRI pulse sequence (see entire document, particularly Abstract). An object of Miyazaki's method is to largely increase contrast between blood and parenchyma compared to the prior method by decreasing the influence of magnetization transfer (MT) effects given blood (performing a blood signal reduction magnetic resonance (MR) excitation sequence that substantially reduces MR signal from blood while substantially retaining parenchymal tissue signal), so that a higher depiction blood flow image or parenchyma image is gained in imaging by which a distinction is made by MT pulses between blood in motion and stationary blood and/or parenchyma (performing a readout MR sequence to acquire a MR signal arising predominantly from parenchymal tissue, column 4, lines 20-27).

With respect to claims 2 and 3, Miyazaki teaches spatially non-selective inversion recovery method (column 2, lines 29-34), which includes applying a spatially non-selective inversion radio frequency pulse, delaying for the inversion time and applying an excitation radio frequency.

With respect to claim 12, Miyazaki teaches a step of generating a reconstructed image from the acquired magnetic resonance signal (column 8, lines 12-24).

With respect to claim 22, Miyazaki teaches as single-shot imaging sequence (column 6, lines 33-45).

However, Miyazaki fails to teach a step of determining a microvascular blood volume parameter based on the acquired MR signal arising predominantly from parenchymal tissue.

Ostergaard teaches that the use of MRI offers the advantage of high resolution images of not only blood flow and volume for microvasculature, but also the possibility of high resolution structural MR images, magnetic resonance angiography (see entire document, particularly p65, lines 13-18).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to use MR method of Miyazaki to determine microvascular blood volume parameter based on the acquired MR images as taught by Ostergaard. The advantage of using high resolution parenchymal tissue image obtained by increased contrast between blood and parenchyma to determine microvascular blood volume provides the motivation to combine teachings of Miyazaki and Ostergaard with a reasonable expectation of success.

19. Claims 4 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miyazaki (U.S. Patent No. 7,254,437 B2, filed Apr. 16, 1999) in view of Ostergaard (WO 00/57777 A1, Oct. 5, 2000) as applied to claims 2 and 3 above, and further in view of

Song et al. (*Magnetic Resonance in Medicine*, 2002, Vol. 47, pp616-620) (hereinafter "Song").

Miyazaki in view of Ostergaard teaches an MR method as set froth above.

However, Miyazaki in view of Ostergaard fails to teach a method, wherein the applying of the inversion radio frequency pulse is performed without an accompanying spatially selective magnetic gradient pulse and b) the applying of the excitation radio frequency pulse is performed with an accompanying spatially selective magnetic field gradient pulse.

Song teaches multislice double inversion pulse sequence for efficient black-blood MRI (see entire document). The double inversion recovery performs better for blood signal nulling than spatial presaturation (p616, right column, 1st full paragraph).

With respect to claim 4, Song teaches applying of the inversion radio frequency pulse is performed without an accompanying spatially selective magnetic gradient pulse; (p616 and Fig. 1) and applying of the excitation radio frequency pulse is performed with an accompanying spatially selective magnetic field gradient pulse. (pp616- 617 and Fig. 1).

With respect to claim 5, Song teaches applying additional inversion radio frequency pulses to maintain blood in a substantially reduced condition. (p616, 2nd paragraph and Fig. 1)

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to use inversion method of Song in the MR method of Miyazaki in view of Ostergaard in order to provide better nulling of the blood signal. The

advantage of better nulling of the blood signal provides the motivation to combine teachings of Miyazaki in view of Ostergaard and Song with a reasonable expectation of success.

20. Claims 13-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miyazaki (U.S. Patent No. 7,254,437 B2, filed Apr. 16, 1999) in view of Ostergaard (WO 00/57777 A1, Oct. 5, 2000) as applied to claims 1 and 12 above, and further in view of Song et al. (*Magnetic Resonance in Medicine*, 2002, Vol. 47, pp616-620) (hereinafter "Song").

Miyazaki in view of Ostergaard teaches an MR method as set froth above.

While Miyazaki further teaches MR readouts at different echo times (Fig. 10), Miyazaki in view of Ostergaard fails to teach a method, further including inducing a physiological perturbation; subsequent to inducing the physiological perturbation, repeating performing the blood signal-reduction magnetic resonance excitation sequence; subsequent to repeating the performing of the blood signal-reduction magnetic resonance excitation sequence, performing a plurality of readout magnetic resonance sequences each having a different echo time to acquire a plurality of magnetic resonance signals corresponding to the plurality of echo times; generating a plurality of perturbation reconstructed images from the acquired plurality of magnetic resonance signals corresponding to the plurality of echo times, the determining of the microvascular blood volume parameter being based on a temporal evolution of a physiological response to the physiological perturbation based on the plurality of perturbation reconstructed images.

Rosenfeld teaches that changes in neuronal activity responsive to the accomplishment of mental and/or physical tasks, such as touching a finger to thumb, are accompanied by physiological changes in regions of the brain associated with and/or controlling the activity (see entire document, particularly column 1, lines 8-15). Physiological changes such as cerebral blood flow, blood volume, blood oxygenation and/or metabolism, occurring in such a region of the brain are made visible by functional MR imaging (fMRI, column 1, lines 8-15). The analysis of Rosenfeld includes performing image registration (alignment), removing trends unrelated to induced neuronal activity (e.g. subject's movement, pulsatile brain motion, pulsatile blood flow, etc.), and constructing a pixel response vector from a time series of the intensity values in the MR images corresponding to a single pixel.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to employ the MR method of Miyazaki in view of Ostergaard to perform a fMRI, in which a physiological perturbation is induced and the blood signal-reduction MR excitation sequence is repeated to acquire a plurality of perturbation reconstructed images corresponding to the plurality of echo times in order to determine of the microvascular blood volume parameter to the physiological perturbation. The advantage of using high resolution parenchymal tissue image obtained by increased contrast between blood and parenchyma to determine microvascular blood volume after physiological perturbation provides the motivation to combine teachings of Miyazaki in view of Ostergaard and Rosenfeld with a reasonable expectation of success.

21. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Miyazaki (U.S. Patent No. 7,254,437 B2, filed Apr. 16, 1999) in view of Ostergaard (WO 00/57777 A1, Oct. 5, 2000) as applied to claims 1 and 12 above, and further in view of Merickel et al. (U.S. Patent No. 4,945,478, July 31, 1990) (hereinafter "Merickel").

Miyazaki in view of Ostergaard teaches an MR method as set froth above.

However, Miyazaki in view of Ostergaard fails to teach a method, generation of normalized reconstructed image by dividing the reconstructed image by a tissue magnetization based on the T1 value of the tissue.

Merickel teaches that average intensity of slices fall off with distance from the surface coil, which requires all of the slices belonging to each of the 3 pulse sequences to be normalized to some standard (see entire document, particularly column 5, lines 16-28). This is accomplished by normalizing (by division) each of the sequences to the mean intensity value of a small set of easily identifiable tissues common to all slices (column 5, lines 16-28). For this data set; skeletal muscle and interstitial tissue is used as the readily identifiable tissues for normalization (column 5, lines 16-28). The mean values for skeletal and interstitial tissue for each pulse sequence are then used to define the set of standard intensity values for these reference tissues, which then allow computation of the T1, pd and T2 normalization scale factors for each slice (column 5, lines 16-28).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to generate normalized reconstructed image by dividing

the reconstructed image by a tissue magnetization based on the T1 value of the tissue as taught by Merickel in the method of Miyazaki in view of Ostergaard. The advantage of normalizing the reconstructed image to a defined standard provides the motivation to combine teachings of Miyazaki in view of Ostergaard and Merickel with a reasonable expectation of success.

22. Claims 18-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miyazaki (U.S. Patent No. 7,254,437 B2, filed Apr. 16, 1999) in view of Ostergaard (WO 00/57777 A1, Oct. 5, 2000) as applied to claims 1 and 12 above, and further in view of Ives et al. (U.S. Patent No. 6,198,958 B1, Mar. 6, 2001) (hereinafter "Ives").

Miyazaki in view of Ostergaard teaches an MR method as set froth above.

Although Miyazaki teaches an MR method for imaging brain as set forth above, Miyazaki in view of Ostergaard fails to teach a method, further including comparing the reconstructed image with a reference image of reference brain region to detect an abnormality of the subject brain region.

With respect to claims 18 and 19, Ives teaches that MRI is a technique for non-invasive imaging and diagnosis of body organs that uses the interaction between a magnetic field and protons in the body to provide images of body tissues (see entire document, particularly column 1, lines 39-47). Functional MRI (fMRI) is a subset of this technology and produces images of activated brain regions by detecting the indirect effects of neural activity on local blood volume, flow, and oxygen saturation (column 1, lines 39-47). A functional map of a patient's brain can be created in response to

stimulation of a particularly area of the brain (column 4, lines 37-51). Development of functional brain maps (relationships between activation of one area of brain and the effect of the activation on other areas of the brain) can significantly improve understanding of the operation of the brain in both normal subjects and those with any type of cognitive disorder (column 4, lines 37-51). fMRI can be used to identify pathway lesions or problems for any type of cognitive disorder by comparing, for example, the MRI of patients with a cognitive disorder with a normal MRI (column 4, lines 52-55).

With respect to claim 20, Ives teaches that the reference brain region is a brain region of a brain other than the subject brain, which corresponds to the subject brain region (column 4, lines 37-55).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to compare the reconstructed image with a reference image of reference brain region as taught by Ives in the method of Miyazaki in view of Ostergaard in order to detect an abnormality of the subject brain region. The advantage of identifying pathway lesions or problems for any type of cognitive disorder provides the motivation to combine teachings of Miyazaki in view of Ostergaard and Ives with a reasonable expectation of success.

23. Claims 23, 24, 29, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miyazaki (U.S. Patent No. 7,254,437 B2, filed Apr. 16, 1999) in view of Ostergaard (WO 00/57777, Oct. 5, 2000) and Merickel (U.S. Patent No. 4,945,478, July 31, 1990).

With respect to claims 23, 29, and 30, Miyazaki teaches a magnetic resonance imaging (MRI) system as set forth above. Miyazaki further teaches acquiring a plurality of reconstructed images corresponding to different echo times (Fig. 10).

With respect to claim 24, Miyazaki teaches an inversion recovery means for performing an inversion recovery magnetic resonance excitation sequence having an inversion time effective to produce a substantially reduced blood signal (column 2, lines 29-34).

However, Miyazaki fails to teach a step of determining a microvascular blood volume parameter based on the acquired MR signal arising predominantly from parenchymal tissue. Miyazaki in view of Ostergaard further fails to teach a method, generation of normalized reconstructed image by dividing the reconstructed image by a tissue magnetization based on the T1 value of the tissue.

Ostergaard teaches that the use of MRI offers the advantage of high resolution images of not only blood flow and volume for microvasculature, but also the possibility of high resolution structural MR images, magnetic resonance angiography as set forth above.

Merickel teaches that average intensity of slices fall off with distance from the surface coil, which requires all of the slices belonging to each of the 3 pulse sequences to be normalized to some standard as set forth above.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to use MR method of Miyazaki to determine microvascular blood volume parameter based on the acquired MR images as taught by

Ostergaard. The advantage of using high resolution parenchymal tissue image obtained by increased contrast between blood and parenchyma to determine microvascular blood volume provides the motivation to combine teachings of Miyazaki and Ostergaard with a reasonable expectation of success.

Further, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to generate normalized reconstructed image by dividing the reconstructed image by a tissue magnetization based on the T1 value of the tissue as taught by Merickel in the method of Miyazaki in view of Ostergaard. The advantage of normalizing the reconstructed image to a defined standard provides the motivation to combine teachings of Miyazaki in view of Ostergaard and Merickel with a reasonable expectation of success.

24. Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over Miyazaki (U.S. Patent No. 7,254,437 B2, filed Apr. 16, 1999) in view of Ostergaard (WO 00/57777, Oct. 5, 2000) and Merickel (U.S. Patent No. 4,945,478, July 31, 1990).as applied to claim 23 above, and further in view of Ives (U.S. Patent No. 6,198,958 B1, Mar. 6, 2001).

Miyazaki in view of Ostergaard and Merickel teaches an MR method as set froth above.

Although Miyazaki teaches an MR method for imaging brain as set forth above, Miyazaki in view of Ostergaard and Merickel fails to teach a method, further including comparing the reconstructed image with a reference image of reference brain region to

detect an abnormality of the subject brain region.

Ives teaches that fMRI can be used to identify pathway lesions or problems for any type of cognitive disorder by comparing, for example, the MRI of patients with a cognitive disorder with a normal MRI as set forth above.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to compare the reconstructed image with a reference image of reference brain region as taught by Ives in the method of Miyazaki in view of Ostergaard and Merickel in order to detect an abnormality of the subject brain region. The advantage of identifying pathway lesions or problems for any type of cognitive disorder provides the motivation to combine teachings of Miyazaki in view of Ostergaard and Merickel and Ives with a reasonable expectation of success.

25. Claims 32-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miyazaki (U.S. Patent No. 7,254,437 B2, filed Apr. 16, 1999) in view of Ostergaard (WO 00/57777 A1, Oct. 5, 2000) as applied to claims 1 and 12 above, and further in view of Song et al. (*Magnetic Resonance in Medicine*, 2002, Vol. 47, pp616-620) (hereinafter "Song").

Miyazaki teaches an MR method as set froth above.

However, Miyazaki fails to teach assessing microvascular blood volume in the parenchymal tissue and acquiring parenchymal MR signal from parenchymal tissue under different parenchymal blood volume perturbing conditions.

Ostergaard teaches that the use of MRI offers the advantage of high resolution

images of not only blood flow and volume for microvasculature, but also the possibility of high resolution structural MR images, magnetic resonance angiography as set forth above.

Rosenfeld teaches that changes in neuronal activity responsive to the accomplishment of mental and/or physical tasks, such as touching a finger to thumb, are accompanied by physiological changes in regions of the brain associated with and/or controlling the activity as set forth above.

With respect to claim 34, Rosenfeld teaches determining change in the vascular space occupancy caused by different perturbations (column 1, lines 8-15).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to use MR method of Miyazaki to determine microvascular blood volume parameter based on the acquired MR images as taught by Ostergaard. The advantage of using high resolution parenchymal tissue image obtained by increased contrast between blood and parenchyma to determine microvascular blood volume provides the motivation to combine teachings of Miyazaki and Ostergaard with a reasonable expectation of success.

Further, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to employ the MR method of Miyazaki in view of Ostergaard to perform a fMRI, in which a physiological perturbation is induced and the blood signal-reduction MR excitation sequence is repeated to acquire a plurality of perturbation reconstructed images corresponding to the plurality of echo times in order to determine of the microvascular blood volume parameter to the physiological perturbation. The

advantage of using high resolution parenchymal tissue image obtained by increased contrast between blood and parenchyma to determine microvascular blood volume after physiological perturbation provides the motivation to combine teachings of Miyazaki in view of Ostergaard and Rosenfeld with a reasonable expectation of success.

Allowable Subject Matter

26. Upon further consideration, the allowable subject matter indicated in the previous Office action dated September 24, 2009 have been withdrawn in view of new grounds of rejections set forth in this Office action.

Double Patenting

27. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

28. Copending Application No. 11/628,089

A. Claims 1-5, 12-15, 18-20, 22, and 32-34 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4-32, and 34-36 of copending Application No. 11/628,089. Although the conflicting claims are not identical, they are not patentably distinct from each other because each recites an MR method including:

- performing a blood signal-reduction MR excitation sequence that substantially reduces a MR signal from blood while substantially retaining parenchymal tissue signal;

- subsequent to the performing of the blood signal-reduction MR excitation sequence, performing a readout MR sequence to acquire a MR signal arising predominantly from parenchymal tissue; and
- determining a microvascular blood volume parameter based on the acquired MR signal arising predominantly from parenchymal tissue.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

B. Claims 23, 24, and 29-31 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4-32, and 34-36 of copending Application No. 11/628,089 in view of Merickel (U.S. Patent No. 4,945,478, July 31, 1990).

The copending application recites an MR method as set forth above. The copending application further recites a system including:

- a blood signal reduction means for performing a blood signal reduction magnetic resonance excitation sequence that substantially reduces a magnetic resonance signal from blood while retaining an effective parenchymal tissue signal;
- a readout means for performing a readout magnetic resonance sequence to acquire a magnetic resonance signal arising predominantly from parenchymal tissue, the readout means operating subsequent to operation of the blood signal reduction

means;

- a reconstruction means for generating a reconstructed image from the acquired magnetic resonance signal; and
- a means for computing a blood volume parameter value from the reconstructed image.

However, the copending application fails to recite generation of normalized reconstructed image by dividing the reconstructed image by a tissue magnetization based on the T1 value of the tissue.

Merickel teaches that average intensity of slices fall off with distance from the surface coil, which requires all of the slices belonging to each of the 3 pulse sequences to be normalized to some standard as set forth above.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to generate normalized reconstructed image by dividing the reconstructed image by a tissue magnetization based on the T1 value of the tissue as taught by Merickel in the method and system of the copending application. The advantage of normalizing the reconstructed image to a defined standard provides the motivation to combine the copending application and Merickel with a reasonable expectation of success.

This is a provisional obviousness-type double patenting rejection.

Response to Arguments

29. Applicant's arguments with respect to claims 1-5, 12-16, 18-20, 22-24, and 29-34 have been considered but are moot in view of the new ground(s) of rejection. However, the following arguments have been addressed as they may apply to the current grounds of rejections set forth above.

Applicant's arguments that Song's method substantially reduces a magnetic resonance signal from both blood and tissue except for a single slice of interest has been fully considered but is not found persuasive. As acknowledged by the applicant on p13 of applicant's remarks, Song teaches nulling of signal from blood. Thus, the imaged slice has signal from the stationary tissue but not from the nulled blood. Therefore, Song does teach substantially reducing a magnetic resonance signal from blood but not tissue as currently recited in the claims.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., while substantially retaining all parenchymal tissue signal) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant's argument that Song's black blood imaging technique would not work with a non-spatially selective inversion recovery because Song uses both spatially non-selective and spatially selective inversion recovery techniques has been fully considered but is not found persuasive. Instant claims recite "a magnetic resonance method including." The transitional term "including", which is synonymous with

"comprising" is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, e.g., *Mars Inc. v. H.J. Heinz Co.*, 377 F.3d 1369, 1376, 71 USPQ2d 1837, 1843 (Fed. Cir. 2004) ("like the term comprising,' the terms containing' and mixture' are open-ended."). See MPEP 2111.03. Therefore, the claimed method does not exclude additional, unrecited elements or method steps such as use of spatially-selective inversion recovery technique in combination with the spatially non-selective inversion recovery technique.

In view of the foregoing response to arguments, the prior art rejections set forth in the current Office action have been maintained.

Since the prior art fulfills all the limitations currently recited in the claims, the invention as currently recited would read upon the prior art.

Conclusion

30. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to UNSU JUNG whose telephone number is (571)272-8506. The examiner can normally be reached on M-F: 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Unsu Jung/
Primary Examiner, Art Unit 3768